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**Title: Severe Central Sleep Apnea in Vici Syndrome**

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Dr. El-Kersh drafted the initial manuscript, and approved the final manuscript as submitted.

Dr. Jungbluth provided results of genetic testing, contributed in editing the manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Prof. Paul Gringras contributed in editing the manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Dr. Senthilvel contributed in drafting the initial manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted.

## Severe Central Sleep Apnea in Vici Syndrome

### **Abstract:**

Vici Syndrome is a rare congenital multisystem disorder due to recessive mutations in the key autophagy regulator *EPG5*. Vici syndrome is characterized by agenesis of the corpus callosum, hypopigmentation, immunodeficiency, cataracts and cardiomyopathy, with variable additional multisystem involvement. Here we report a 5-year-old girl presenting with global developmental delay, seizures, callosal agenesis, cataracts, sensorineural hearing loss, hypopigmentation, and immunodeficiency with low CD4 count and recurrent infections. *EPG5* sequencing (prompted by suggestive clinical features) revealed a homozygous missense mutation, c.1007A>G; p.Gln336Arg.

The patient was referred to our center for evaluation of nocturnal apnea. Overnight polysomnography showed severe central sleep apnea (CSA) with an overall apnea-hypopnea index of 100.5 events per hour of sleep (central apnea index of 97.5, mixed apnea index of 2, and obstructive hypopnea index of 1). The patient responded to bi-level positive airway pressure therapy with a backup rate with normalization of the apnea-hypopnea index, and maintenance of oxygen saturation above 90%. Despite successful control of the severe CSA, the patient was eventually started on nocturnal oxygen therapy due to excessive upper airway secretions and the high risk of possible aspiration with positive airway pressure therapy. This is the first report of *EPG5*-related Vici syndrome associated with CSA. We discuss the polysomnographic findings in our patient in the context of a brief literature review of the reported sleep abnormalities in Vici syndrome.

## **Introduction:**

Vici syndrome (OMIM 242840) is a rare congenital syndrome with extensive multisystem involvement due to recessive mutations in *EPG5* on chromosome 18q12.3, encoding the key autophagy regulator ectopic P-granules protein 5 (EPG5).<sup>1</sup> Vici syndrome was originally described in 1988 by Dionisi-Vici et al. in two brothers but with less than 30 cases reported to date, the phenotypical spectrum is still evolving.<sup>1-3</sup>

## **Case Report:**

A 5-year-old girl diagnosed with Vici syndrome presented to our sleep center for evaluation of frequent short episodes of witnessed non-life-threatening nocturnal apnea. She was born via Cesarean section at 37 weeks' gestation to consanguineous first cousin parents. Delivery was complicated by meconium aspiration. Birth weight was 2.27 kg (<3<sup>rd</sup> percentile), length was 49.5 cm (57<sup>th</sup> percentile), and occipital frontal circumference was 34.3 cm (62<sup>nd</sup> percentile). She had a history of global developmental delay, seizures, bilateral cataracts, sensorineural hearing loss, biopsy-proven myopathy, and immunodeficiency with low CD4 count complicated by recurrent respiratory infections. She also had a transient dilated cardiomyopathy during an acute illness at the age of one year. Her mother had a history of obstructive sleep apnea and two first trimester spontaneous abortions; an older sibling was healthy.

Previous investigations included analysis of the oculocutaneous albinism type 2 (*OCA2*) gene, revealing no mutations, and an examination of peripheral blood smears, requested under the suspicion of Chediak-Higashi syndrome but not showing any of the giant neutrophil granules suggestive of the latter. Brain magnetic resonance imaging (MRI) showed findings consistent with Vici syndrome, including agenesis of corpus callosum, colpocephaly, and atrophy of the optic nerves, pons, medulla, cerebellum, and cerebral hemispheres (Figure 1). Further genetic

testing prompted by suggestive clinical features revealed homozygosity for the *EPG5* c.1007A>G; p.Gln336Arg missense mutation, previously reported by Cullup et al.<sup>1</sup> Key clinical and genetic features from our patient have been previously reported.<sup>1</sup>

On examination at presentation to our center, height was 104 cm (22<sup>nd</sup> percentile) and weight was 15.5 kg (13<sup>th</sup> percentile). She did have no speech. There was generalized hypotonia and she couldn't walk or sit without support. She had evidence of generalized hypopigmentation of the eyes, hair, and skin (Figure 2). She had a gastrostomy tube in place because of feeding difficulties. Oral examination revealed a normal tongue, Mallampati class IV, grade 2 tonsils, and a high arched palate with no micrognathia or maxillary retrusion.

The patient underwent an overnight diagnostic polysomnography (PSG) (Table 1) using Respiration Alice system (Pittsburgh, PA). The PSG and sleep associated events were scored according to American Academy of Sleep Medicine (AASM) scoring guidelines.<sup>4</sup> The patient had a total of 769 events including 746 central apneas, 15 mixed apneas, and 8 hypopneas with an overall apnea hypopnea index (AHI) of 100.5 events per hour of sleep (central apnea index of 97.5, mixed apnea index of 2, and obstructive hypopnea index of 1) (Figure 3).

Minimum oximetry value was 54% and the total time spent with O<sub>2</sub> saturation below 89% was 111.7 minutes. Transcutaneous carbon dioxide monitoring showed a mean PaCO<sub>2</sub> of 46 mmHg. The PaCO<sub>2</sub> was elevated above 50mmHg for almost 20% of the total sleep time (TST). The patient was not receiving any narcotics and her cardiac echocardiography showed normal cardiac anatomy and function with no evidence of pulmonary hypertension. High resolution chest CT showed no evidence of interstitial lung disease.

Subsequently, the patient underwent an overnight titration study (Table 1). At bi-level PAP settings of 14/7 cmH<sub>2</sub>O in spontaneous/timed mode with a backup rate of 12 breaths per minute

the apnea hypopnea and arousal indices were normalized, and oxygen saturation was maintained above 90%. It was difficult for the patient to use positive airway pressure therapy due to excessive upper airway secretions, despite treatment with Glycopyrrolate, and the high risk of aspiration. After extensive discussion with the parents and considering the patient's overall prognosis, a palliative management approach was chosen, including nocturnal oxygen at 1.5 liters per minutes to keep her saturation above 90%. Unfortunately, our patient passed away at the age of 6 years as a consequence of recurrent infections. An autopsy was not performed.

### **Discussion:**

Vici syndrome is a rare and severe congenital multisystem disorder with markedly reduced life expectancy. In the largest cohort study of Vici syndrome patients with confirmed *EPG5* mutations, only half of them were alive at the time of the last follow up.<sup>1</sup> The most common identifiable causes of death were progressive cardiac failure and recurrent infections secondary to the associated combined immunodeficiency.<sup>1</sup>

Sleep abnormalities in Vici syndrome remain to be elucidated. Actigraphy and PSG were performed in two siblings with Vici syndrome. The actogram demonstrated a delay in the circadian rhythm in one patient possibly due to severe visual impairment. The PSG in both patients showed impaired phasic REM sleep parameters in setting of preserved percentage of REM sleep, and increased muscle atonia during NREM sleep. In both patients the brain MRI showed corpus callosum agenesis, mild cerebral atrophy, and opercular hypoplasia but no brain stem lesions.<sup>5</sup>

In patients with Vici syndrome, the reported facial abnormalities, hypotonia, and laryngomalacia can all predispose to obstructive sleep apnea (OSA).<sup>6</sup> Despite these reported anomalies, only one

case of Vici syndrome with OSA and mild desaturations was described. The patient's brain MRI showed corpus callosum agenesis, pontine and cerebellar hypoplasia.<sup>7</sup>

To our knowledge, this is the first case of Vici syndrome featuring CSA. Severe neurological involvement that included both the pons and medulla in our patient, evidenced by brain MRI, is a plausible cause in the pathogenesis of the central sleep apnea but the exact mechanism cannot be extrapolated from a single case. Besides absence of corpus callosum, additional central nervous system abnormalities were reported in 19 out of 27 patients diagnosed with Vici syndrome.

These abnormalities included cerebellar and pontine hypoplasia, ventricular dilatation with white matter atrophy, heterotopias, abnormal septum pellucidum, and schizencephaly.<sup>(1,3)</sup> In absence of sleep studies in most of the Vici syndrome patients reported, sleep related breathing disorders including CSA cannot be excluded.

Although the awake respiratory rate was lower than expected for age, our patient maintained awake PaCo<sub>2</sub> level below 50mmHg with no elevation of serum bicarbonate levels. During sleep, there was further reduction of the respiratory rate with periods of hypercapnia. Although this can represent an element of sleep related hypoventilation, the total duration spent with PaCo<sub>2</sub> above 50mmHg was less than 25% of the TST which is required to score pediatric sleep related hypoventilation according to AASM scoring guidelines.<sup>4</sup>

Another observation was the predominance of stage N3 non-rapid eye movement. Our patient spent 98.8% and 96.8% of her TST in stage N3 non-rapid eye movement during the diagnostic and the titration studies, respectively. Subjects with corpus callosum agenesis tend to have more slow-wave sleep, less inter-hemispheric electroencephalography coherence, and ultradian rhythm disturbances.<sup>8</sup> Despite these findings in acallosal subjects, slow-wave sleep predominance was not described before among the polysomnographic findings in Vici syndrome.<sup>5,7</sup>



Although our patient was not receiving any REM sleep-suppressant medications, she did not have any REM sleep either during the diagnostic or the titration study. It is plausible that the absence of REM sleep in our patient could have been related to her pontine atrophy, considering that the pons plays an essential role in generation of REM sleep during which the central nervous system (CNS) cholinergic activity predominates.<sup>9</sup> Absence of REM sleep may suggest an impairment of CNS cholinergic system as well. Although REM sleep percentage was reported to be preserved in two siblings with Vici syndrome, both of them did not have evidence of brain stem involvement on brain MRI in contrast to our patient.<sup>5</sup>

Pitt–Hopkins syndrome and familial agenesis of the corpus callosum are two conditions in which apneic spells were described in association with callosal agenesis. In both syndromes there was evidence of respiratory rhythm disturbances.<sup>10,11</sup> In Pitt–Hopkins syndrome the apneic spells were confirmed to be central apneas via polygraphic recording in one patient who did not have signs of brain stem abnormalities on imaging.<sup>10</sup> In familial callosal agenesis, the apneic spells were clinically described and postmortem examination showed marked brain stem spongiosis, among other findings.<sup>11</sup> The apneic spells in these syndromes can be related to episodes of hyperventilation (post-hyperventilation apnea) in Pitt-Hopkins syndrome or to brain stem involvement in familial callosal agenesis.<sup>10, 11</sup> Although animal studies suggest a possible role for the corpus callosum in functional integration of respiratory centers on both sides, the clinical implication of this observation in acallosal subjects is yet to be elucidated.<sup>12</sup>

The potential for CSA to worsen heart failure in Vici syndrome patients with undiagnosed central apneas is not to be underestimated. The pathophysiological consequences of CSA adversely affect left ventricular structure, function and can worsen heart failure via several mechanisms that include increasing expression of pro-inflammatory and vasoconstrictor genes,

augmenting nocturnal sympathetic activity, and via changes in intra-thoracic pressure that can increase the afterload and oxygen consumption on an already compromised left ventricle. <sup>(13-16)</sup>

Although there are short-term suggestions that treatment of CSA might improve cardiac function, there are however no robust studies to show the long term impact of treatment, particularly in children with rare disorders.

In conclusion, we describe the first case of CSA associated with *EPG5*-related Vici syndrome.

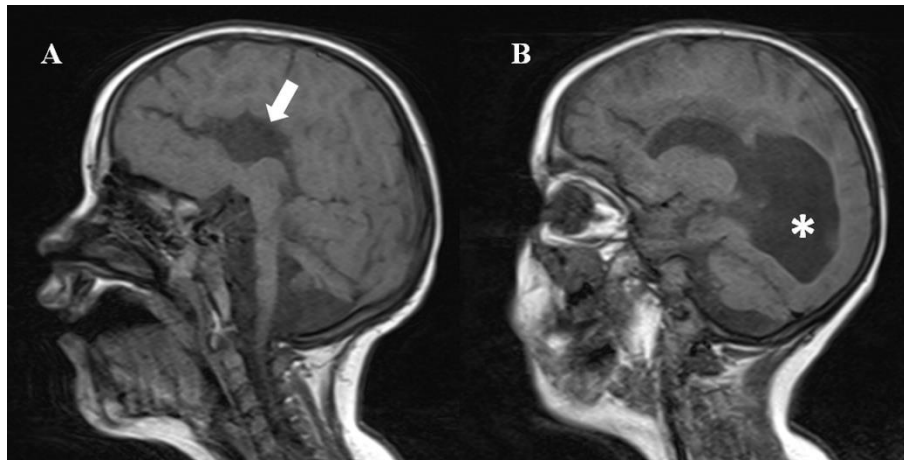
Our observation suggests that in addition to the associated cardiomyopathy and combined immunodeficiency, CSA has to be considered as another important and potentially treatable cause of morbidity and mortality in *EPG5*-related Vici syndrome. More studies are needed to further investigate sleep abnormalities in *EPG5*-related Vici syndrome and their consequences.

Finally, our observations suggest an intriguing link between certain sleep disorder phenotypes and neurodevelopmental disorders involving structural abnormalities of the corpus callosum and the pons.

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**Figure1:**

Brain MRI sagittal T1-weighted images show agenesis of corpus callosum (A; arrow), colpocephaly (B; \*), and marked atrophy of pons, medulla, cerebellum and cerebral hemispheres.



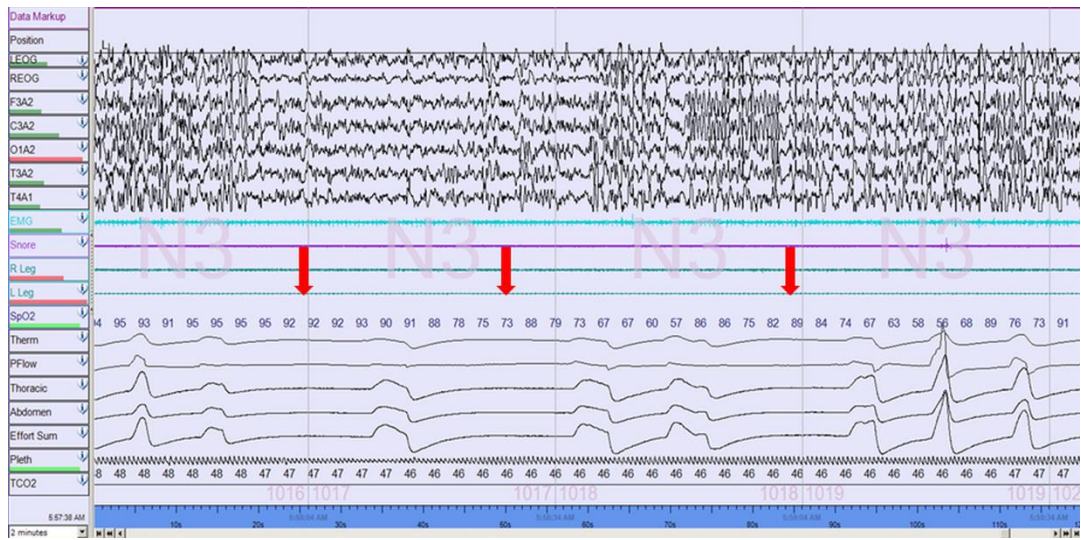
**Figure 2:**

The patient at the age of 3 years. (Consent was obtained from the parents)

**Table1**: Sleep architecture during the diagnostic and the titration study

<b>Parameter</b>	<b>Diagnostic study</b>	<b>Titration study</b>
Recording time (min)	520	486
Total sleep time (TST) (min)	459	411.5
Sleep efficiency (%)	88	84
Sage N1 (%)	0	0
Stage N2 (%)	0.8	3.2
Stage N3 (%)	98.9	96.8
Stage REM (%)	0	0
Highest tcpco2*	59mmHg	46mmHg

\*tcpco2, transcutaneous carbon dioxide



**Figure 3:**

A 2-minute polysomnographic recording during stage N3 non-rapid eye movement shows central apneas (red arrows) (transcutaneous PaCo2 shows PaCo2 levels below 50mmHg).